

**KLI0001-100
PATENT APPLICATION**

**Serial No.: 09/801,470
Filed: March 8, 2001**

IN THE CLAIMS:

1. (previously presented) A method of diagnosing an abnormality in endometrial glandular development in a woman comprising the step of:

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or after day 20 of an idealized 28 day menstrual cycle from a woman;

wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates endometrial glandular developmental arrest, and/or

expression of cyclin E of greater than 1+ staining intensity in the cytoplasm of greater than 10% of the gland cells indicates endometrial glandular developmental arrest.

2. (original) The method of claim 1 wherein the expression of cyclin E is detected by an immunohistochemistry assay.

3. (original) The method of claim 1 wherein the cycle day is determined by examining the stroma cells in the sample.

4. (original) The method of claim 1 wherein expression of cyclin E is detected in the nuclei of greater than 10% of the gland cells in the sample is indicative of endometrial glandular developmental arrest.

5. (original) The method of claim 1 wherein the cycle day is day 24 of an idealized 28 day menstrual cycle.

6. (original) The method of claim 1 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample.

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7. (original) The method of claim 1 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

8. (original) The method of claim 1 further comprising the step of detecting the expression mouse ascites golgi mucin MAG in the gland cells in a serial section of the sample.

9. (original) The method of claim 1 further comprising the steps of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample and either detecting the expression of progesterone receptor in the gland cells in a serial section of the sample or detecting the expression of MAG in the gland cells in a serial section of the sample or both.

10. (original) The method of claim 1 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

11. (original) The method of claim 1 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from day 15 an idealized 28 day menstrual cycle from the woman.

12. (original) The method of claim 1 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

13. (original) The method of claim 1 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from before day 17 of an idealized 28 day menstrual cycle from the woman wherein expression of p27 is indicative of accelerated endometrial glandular development.

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14. (original) The method of claim 1 further comprising the step of detecting expression of progesterone receptor in the gland cells in an endometrial tissue sample from before day 18 of an idealized 28 day menstrual cycle from the woman.

15. (original) The method of claim 1 further comprising the step of detecting the expression MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

16. (original) The method of claim 1 further comprising at least two of the following steps of:

- a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- b) detecting the expression of p27 in the nuclei of gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- c) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- d) detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

17. (previously presented) A method of predicting abnormal endometrial glandular development comprising the steps of:

detecting the level of p27 in the nuclei of cells in a sample of endometrial tissue from day 10-18 of an idealized 28 day menstrual cycle from a woman

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and

comparing the level of expression with an expected level of expression;
wherein detection of elevated levels of p27 in the sample is predictive that the woman
will be diagnosed with endometrial glandular developmental arrest.

18. (original) The method of claim 17 wherin the expression of p27 is detected by an immunohistochemistry assay.

19. (original) The method of claim 17 wherein the cycle day is determinded by examining the stroma and gland cells in the sample

20. (original) The method of claim 17 wherein the cycle day is day 15 of a idealized 28 day menstrual cycle.

21. (original) The method of claim 17 further comprising the step of detecting the expression of cyclin E in the nuclei and/or cytoplasm of gland cells in a serial section of the sample.

22. (original) The method of claim 17 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

23. (original) The method of claim 17 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample.

24. (original) The method of claim 17 further comprising at least two of the following steps of:

- a) detecting the expression of cyclin E in the nuclei and /or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

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- b) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- c) detecting expression of MAG in the gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

25 – 63. (cancelled)

64. (previously presented) A method of diagnosing an abnormality in endometrial glandular development in a woman suspected of being infertile comprising the step of:

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or after day 20 of an idealized 28 day menstrual cycle from said woman;

wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates endometrial glandular developmental arrest, and/or

expression of cyclin E of greater than 1+ staining intensity in the cytoplasm of greater than 10% of the gland cells indicates endometrial glandular developmental arrest.

65. (previously presented) The method of claim 64 wherein the expression of cyclin E is detected by an immunohistochemistry assay.

66. (previously presented) The method of claim 64 wherein the cycle day is determined by examining the stroma cells in the sample.

67. (previously presented) The method of claim 64 wherein expression of cyclin E is detected in the nuclei of greater than 10% of the gland cells in the sample is indicative of endometrial glandular developmental arrest.

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68. (previously presented) The method of claim 64 wherein the cycle day is day 24 of an idealized 28 day menstrual cycle.

69. (previously presented) The method of claim 64 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample.

70. (previously presented) The method of claim 64 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

71. (previously presented) The method of claim 64 further comprising the step of detecting the expression mouse ascites golgi mucin MAG in the gland cells in a serial section of the sample.

72. (previously presented) The method of claim 64 further comprising the steps of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample and either detecting the expression of progesterone receptor in the gland cells in a serial section of the sample or detecting the expression of MAG in the gland cells in a serial section of the sample or both.

73. (previously presented) The method of claim 64 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

74. (previously presented) The method of claim 64 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from day 15 an idealized 28 day menstrual cycle from the woman.

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75. (previously presented) The method of claim 64 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

76. (previously presented) The method of claim 64 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from before day 17 of an idealized 28 day menstrual cycle from the woman wherein expression of p27 is indicative of accelerated endometrial glandular development.

77. (previously presented) The method of claim 64 further comprising the step of detecting expression of progesterone receptor in the gland cells in an endometrial tissue sample from before day 18 of an idealized 28 day menstrual cycle from the woman.

78. (previously presented) The method of claim 64 further comprising the step of detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

79. (previously presented) The method of claim 64 further comprising at least two of the following steps of:

- a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- b) detecting the expression of p27 in the nuclei of gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- c) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

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d) detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
wherein said two or more steps are performed on serial sections of the sample.

80. (previously presented) A method of claim 64 wherein said woman is undergoing a hormonal protocol to produce a mock cycle.

81. (previously presented) A method of claim 1 wherein said woman is undergoing a hormonal protocol to produce a mock cycle.

82. (previously presented) A method of claim 17 wherein said woman is undergoing a hormonal protocol to produce a mock cycle.

83. (previously presented) The method of claim 80 wherein the expression of cyclin E is detected by an immunohistochemistry assay.

84. (previously presented) The method of claim 80 wherein the cycle day is determined by examining the stroma cells in the sample.

85. (previously presented) The method of claim 80 wherein expression of cyclin E is detected in the nuclei of greater than 10% of the gland cells in the sample is indicative of endometrial glandular developmental arrest.

86. (previously presented) The method of claim 80 wherein the cycle day is day 24 of an idealized 28 day menstrual cycle.

87. (previously presented) The method of claim 80 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample.

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88. (previously presented) The method of claim 80 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

89. (previously presented) The method of claim 80 further comprising the step of detecting the expression mouse ascites golgi mucin MAG in the gland cells in a serial section of the sample.

90. (previously presented) The method of claim 80 further comprising the steps of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample and either detecting the expression of progesterone receptor in the gland cells in a serial section of the sample or detecting the expression of MAG in the gland cells in a serial section of the sample or both.

91. (previously presented) The method of claim 80 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

92. (previously presented) The method of claim 80 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from day 15 an idealized 28 day menstrual cycle from the woman.

93. (previously presented) The method of claim 80 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

94. (previously presented) The method of claim 80 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from before day 17 of an idealized 28 day menstrual cycle from the woman wherein expression of p27 is indicative of accelerated endometrial glandular development.

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95. (previously presented) The method of claim 80 further comprising the step of detecting expression of progesterone receptor in the gland cells in an endometrial tissue sample from before day 18 of an idealized 28 day menstrual cycle from the woman.

96. (previously presented) The method of claim 80 further comprising the step of detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

97. (previously presented) The method of claim 80 further comprising at least two of the following steps of:

- a. detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- b. detecting the expression of p27 in the nuclei of gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- c. detecting expression of progesterone receptor in gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- d. detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

98. (previously presented) A method of predicting abnormal endometrial glandular development in a woman suspected of being infertile comprising the steps of:

detecting the level of p27 in the nuclei of cells in a sample of endometrial tissue from day 10-18 of an idealized 28 day menstrual cycle from said woman, and

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comparing the level of expression with an expected level of expression; wherein detection of elevated levels of p27 in the sample is predictive that the woman will be diagnosed with endometrial glandular developmental arrest.

99. (previously presented) The method of claim 98 wherein the expression of p27 is detected by an immunohistochemistry assay.

100. (previously presented) The method of claim 98 wherein the cycle day is determined by examining the stroma, and gland cells in the sample.

101. (previously presented) The method of claim 98 wherein the cycle day is day 15 of an idealized 28 day menstrual cycle.

102. (previously presented) The method of claim 98 further comprising the step of detecting the expression of cyclin E in the nuclei and /or cytoplasm of gland cells in a serial section of the sample.

103. (previously presented) The method of claim 98 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

104. (previously presented) The method of claim 98 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample.

105. (previously presented) The method of claim 98 further comprising at least two of the following steps of:

- a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- b) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

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c) detecting the expression of MAG in the gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

106. (previously presented) A method of claim 98 wherein said woman is undergoing a hormonal protocol to produce a mock trial.

107. (previously presented) The method of claim 106 wherein the expression of p27 is detected by an immunohistochemistry assay.

108. (previously presented) The method of claim 106 wherein the cycle day is determined by examining the stroma, and gland cells in the sample.

109. (previously presented) The method of claim 106 wherein the cycle day is day 15 of an idealized 28 day menstrual cycle.

110. (previously presented) The method of claim 106 further comprising the step of detecting the expression of cyclin E in the nuclei and /or cytoplasm of gland cells in a serial section of the sample.

111. (previously presented) The method of claim 106 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

112. (previously presented) The method of claim 106 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample.

113. (previously presented) The method of claim 106 further comprising at least two of the following steps of:

a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

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- b) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;
- c) detecting the expression of MAG in the gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman; wherein said two or more steps are performed on serial sections of the sample.